REMARKS/ARGUMENTS

Reconsideration of this application is requested. Claims 1-9, 13, 14, 18, 19 and 21 are under active examination; claim 20 is withdrawn from consideration as directed to non-elected subject matter.

The first two items of the Official Action, 2 and 3, are provisional obviousness-type double patenting rejections based upon two co-pending applications assigned to the owners of the present application. As these are both provisional rejections, applicants will hold in abeyance a full and complete response until such time as the claims of the present application are indicated to be allowable. Applicants reserve their rights to address these provisional rejections on the merits at a later date.

The balance of the Official Action deals with a series of prior art-based rejections. With reference to the objection that claims 1, 6, 8, 9, 13, 14, 18 and 21 lack of novelty over Nsereko (Biomaterials 2002), this rejection is overcome by limiting the porous carrier in present claims 1 and 18 to porous silicon from present claims 3 and 19, respectively. Corresponding changes have been made to claims 2 and 4.

The Examiner asserts that Nsereko discloses the administration of a porous material and paclitaxel directly into a tumor as a method of treating cancer. Applicants point out, however, that the porous material used in Nsereko is organic chitin and chitin-pluronic microparticles, prepared from chitosan solution (*see* the abstract and the materials and methods section on page 2724). There is no disclosure or suggestion in Nsereko that the porous carrier material may be silicon and so we would submit that Nsereko does not render proposed amended claims 1 and 18 lacking in novelty.

Counsel observes that claims 3 and 19 were not included in the anticipation rejection, thus by incorporating claims 3 and 19 into independent claims 1 and 18, by definition this rejection has been overcome.

Turning to the rejections under 35 USC 103 in items 9-12 of the Action, applicants note that claims 1-4, 6, 8, 9, 13, 14, 18, 19 and 21 are rejected over the assignee's earlier 'brachytherapy' filing (Canham, WO 02/067998) in view of Nsereko and/or Straub (US 6,601,317) and further in view of Canham (US 6,322,895).

These rejections are not well founded for the following reasons:

Canham WO 02/067998 and Nsereko

As the Examiner points out, Canham (WO 02/067998) discloses a product comprising an anticancer agent and/or a cytotoxic drug and a silicon component which may be porous silicon. As the Examiner also acknowledges, Canham WO 02/067998 makes no mention of direct intra-tumoral administration (rather, implantation of the implant into the organ in which the tumor is located is envisaged) nor does the list of suitable cytotoxic drugs mentioned on page 8, lines 25-29 of the specification include chlorambucil or paclitaxel (which are the subject of present claim 8).

The Examiner asserts that injection directly into the tumor and the use of paclitaxel as cytotoxic agent would have been obvious in view of Nsereko. However, applicants disagree that Nsereko provides the missing motivation necessary to arrive at the present invention. As discussed above, Nsereko is concerned with an entirely different carrier material and the average skilled reader would have no reason to consider the teaching of Nsereko relevant to chemotherapy products containing silicon as a delivery vehicle. Applicants submit that the skilled person looking to provide alternative silicon containing compositions to those disclosed in Canham for use in the treatment of cancer by chemobrachtherapy would simply not look to Nsereko for guidance — and even if they did, would have no reason to predict the presently observed advantages that formulating cytotoxic drug in a porous silicon carrier would allow the site-specific administration of cytotoxic drugs at dosage levels in excess of the LD_{50} of the free drug without significant mortality.

According to Canham WO 02/067998, the advantages of using porous silicon in the preparation of an implant for brachytherapy are that it can readily be processed by standard microfabrication techniques (page 4, lines 8-10), it is resorbable allowing repeated administration (page 6, lines 29-30), the particle density of the silicon microparticles can be controlled by altering the porosity of the silicon (which is important in determining the success of treating liver cancer by administration of microparticles to the hepatic artery -- *see* page 5, lines 19-22), it may be transmuted into radioactive compositions dependent upon the cancer to be treated (*see* page 5, lines 11-13) and it localizes the radionucleotide to the region of the tumor until the radioactivity has decayed to a safe level (*see* page 6, lines 24-32). Canham in no way suggests that the use of a porous silicon carrier would allow such a high dose of drug as the

LD5O (or even higher -- *see* Example 4, page 24, line 27-page 25, line 10 which describes the delivery of 2 x LD_{50} of chlorambucil by porous silicon to achieve significant tumor reduction without significant animal mortality).

The Examiner argues that although neither Canham nor Nsereko disclose the dose delivered, there is no evidence to show that the dosage delivered from the silicon microparticles of Canham would not be higher than the LD_{50} of the free cytotoxic drug and therefore that delivery of such a high dose would be inherent. Applicants disagree and submit that there is simply no basis for this other than hindsight analysis based on knowledge of the present invention.[1] The average skilled person would well understand the intention with a targeted delivery system such as described in Canham would be to deliver lower doses than for oral administration, if anything, and certainly the delivery of dosages which are greater than the LD5O would not be envisaged.

The finding that by means of the present method, dosages considerably in excess of the LD5O of the free drug can be administered intratumorally without significant mortality therefore represents a completely unexpected result which could not have been predicted from Canham alone or in combination with Nsereko.

Canham (US 6,322,895) does not provide the motivation missing from Canham WO 02/067998 and Nsereko to arrive at the presently claimed method. At best, the combination of Canham WO 02/067998 and Canham US 6,322,895 would lead the average skilled person to consider using mesoporous silicon as a porous carrier material. For the reasons discussed above in relation to Nsereko, there would still be no motivation to consider direct intratumor administration and no expectation that the delivery of dosages which are significantly greater than the LD_{5O} could be achieved.

[1] An obviousness rejection must rest on a sound factual basis with these facts being deduced without hindsight reconstruction of the invention from the prior art. The Examiner may not, because of doubt that the invention is patentable, resort to speculation, unfounded assumption, or hindsight reconstruction to supply deficiencies in the factual basis for the rejection. *See In re Warner*, 379 F.2d 1011, 1017 (CCPA 1967). One cannot employ hindsight by using the applicant's own disclosure as a blueprint to reconstruct the claimed invention from the isolated teachings of the prior art. *See, e.g., Grain Processing Corp. v. American Maize-Products Co.*, 840 F.2d 902, 907 (Fed. Cir. 1988)

Canham WO 02/067998 and Straub (US 6,610,317)

Although Straub (US 6,610,317) describes paclitaxel in porous matrix form, this matrix comprises hydrophilic excipients and a wetting agent. There is no disclosure or suggestion of a porous silicon carrier and so we would submit that the average skilled man looking to provide alternative formulations and methods to Canham WO 02/067998 would not look to Straub for guidance. Again, Canham US 6,322,895 does not provide the missing motivation.

For the above reasons it is respectfully submitted that the pending claims define novel and inventive subject matter. Reconsideration and allowance are solicited. The examiner is urged to contact the undersigned if only double patenting issues remain for resolution.

Respectfully submitted,

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